What Are the Effects of Weight Management Pharmacotherapy on Lipid Metabolism and Lipid Levels?

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Liver lipids

Blood Lipids

Liver

Dietary lipid

GI Tract

Liver lipids

Hormones
- Insulin
- Catechols
- GH
- Leptin

Brain

Adipose Tissue
- CO₂
- IMTG

Muscle
Weight Gain and CVD

Lean

Obesity

Resistance

Inflammation

Diabetes

Coronary Artery Disease

Hyperlipidemia

Hypertension

Strokes

Time
Summary Points

• Lipid lowering drugs have a bigger effect on serum lipid levels than obesity treatments.
• Obesity treatments are not FDA approved for lipid lowering.
• Obesity is likely involved in the pathogenesis of CVD and other diseases and treatment is advocated widely in guidelines.
• Patients often inquire about help with weight loss
• As lipid specialists you should decide what role weight loss plays in your practice and how to talk to your patients about their options.
Game plan

• Phen/fen as a model…lessons?
• Sibutramine as a model…lessons?
• Weight loss agents
  – Orlistat
  – Phentermine/topiramate ER
  – Lorcaserin
  – Naltrexone ER/Bupropion ER
  – Liraglutide 3mg
• Some final thoughts
Phen/fen Weight loss

Figure 1: Shown is the 20% weight loss with fenfluramine and either mazindol or phentermine in the 220 patients compliant to their medical regimen at 6 months and 60 patients compliant to their medical regimen at 1 year.

Obesity Research 1999: 7; 523-531
Phen/fen: Lipids

- Tg levels went down 2.5%/weight lost
- LDL levels went down 0.9%/weight lost

| Medication status, weight loss, percent weight loss, and time of minimal medication dose |
|---------------------------------|------------------|------------------|------------------|
|                                 | Time (weeks)     | Weight loss (kg) | %                |
| Diabetes (Rx with insulin)     | 8.0±2.1          | 9.9±.9           | 9.0±1.7          |
| Diabetes (Rx with sulfonylurea)| 5.7±1.1          | 7.6±.9           | 8.2±1.7          |
| Hyperlipidemia (Rx with meds)  | 6.0±2.4          | 8.2±1.7          | 9.7±2.1          |
| Hypertension (Rx with meds)    | 10.9±1.2         | 13.2±.6          | 10.6±0.9         |
|                                 |                   |                  | Discontinued     |
|                                 |                   |                  | Reduced          |
|                                 |                   |                  | Unchanged        |
| Diabetes (Rx with insulin)     | 100              | 0                | 0                |
| Diabetes (Rx with sulfonylurea)| 100              | 0                | 0                |
| Hyperlipidemia (Rx with meds)  | 64               | 0                | 36               |
| Hypertension (Rx with meds)    | 56               | 30               | 14               |

The amount of weight loss and the time at which the optimal improvement occurred in subjects on medications for obesity associated disease.

Obesity Research 1999: 7; 523-531
Sibutramine: Weight loss

Figure 2: Mean bodyweight changes during weight-loss and weight-maintenance phases

Lancet 2000:356; 2119-25
Sibutramine: Lipids

Lancet 2000:356; 2119-25
Sibutramine: CVD risk
the SCOUT trial

Sibutramine: Lessons learned?

• SCOUT trial included high risk patients that would not otherwise have been treated.
• Continued medication even if they did not lose weight
• 2012 Case/control study >6000 pts in UK and Germany showed significantly lower ASCVD risk in sibutramine users
• 2015 case/control study >23,000 pts in UK increased risk in those with CVD (DM, DM+1RF) but not in those without.

Tyczynski Drug Saf 2012. 35:629-44
1º Drug Treatment of Obesity

- Current medications 5-12% wt loss
- Likely will need to use long term.
- Typically not paid for by insurance so cost is a big issue for patients.
- Issues of FDA approval, long term safety, and efficacy.
- Meds: phentermine, orlistat, phentermine/topiramate ER, lorcaserin, Naltrexone SR/Bupropion SR
Orlistat

- Thousands of patients studied up to 4 years of exposure.
- Approved for long term use
- 5-8% weight loss on average
- Side effects: Oily stools, diarrhea, urgency, theoretically fat soluble vitamin deficiency
- Safest weight loss medication
Effect of Orlistat on Body Weight

Orlistat + Fenofibrate effects on sdLDL-C

Fig. 1. Subjects with phenotype nonA at baseline and after 6 months of treatment (the six patients who did not complete the study are not included). O: orlistat; F: micronised fenofibrate; OF: orlistat + micronised fenofibrate. *p < 0.001 vs. baseline. &p < 0.05 vs. O group.
Phentermine/Topiramate (Qsymia, Vivus)

- Combination gives greater efficacy with fewer side effects
- Doses 7.5/46 mg and 15/92 mg phentermine/topiramate
- Side effects: dry mouth, paraesthesias, insomnia, dizziness, anxiety, irritability and disturbance in attention
Phentermine/Topiramate

- Topiramate teratogenic risk: pregnancy test on starting and monthly while using.
- Most effective medication available 10-12% weight loss.
- Reduces blood pressure, glucose, insulin, triglycerides and raises HDL.
- Unclear if physicians will prescribe off label using generic phentermine and topiramate.
Phen/Top (Qsymia) 2 year data on Weight: SEQUEL Trial

Am J Clin Nutr 2012;95:297–308
Phen/Top (Qsymia) 2 year data on Lipids: SEQUEL Trial

Am J Clin Nutr 2012;95:297–308
Lorcasarin

- Serotonin 2C receptor agonist, activates POMC neurons which leads to \( \alpha \)-MSH activation of MC4R leading to satiety
- Dose: 10 mg twice daily
- Previous serotonin agonists fenfluramine and dexfenfluramine caused cardiac valve disease
- 2C receptor only in the brain not in heart
- Studies in 1-2,000 people for up to 2 years do not show evidence of valvulopathy with lorcasarin.

Yanovski SZ, Yanovski JA. JAMA. 2014;311:74-86
Lorcasarin

• Weight loss: 4-6% not much better than phentermine or orlistat
• Side effects: minimal, headache, dizziness and nausea (rare priapism, monitor for depression), best side effect profile
Lorcaserin (Belviq): Weight Effects

BLOOM Study

Figure 1. Effects of the Study Drug on Body Weight, According to Study Group.

# Lorocasarin: Lipid Effects

**BLOOM Study**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Intention-to-Treat Analysis with LOCF Imputation</th>
<th>Repeated-Measures Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lorocasarin (N=1538) Placebo (N=1499) P Value</td>
<td>Lorocasarin (N=1538) Placebo (N=1499) P Value</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
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<tr>
<td>Systolic</td>
<td>−1.4±0.3</td>
<td>−1.5±0.3</td>
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<tr>
<td>Diastolic</td>
<td>−1.1±0.2</td>
<td>−1.3±0.3</td>
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<tr>
<td>Cholesterol (%)</td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>−0.90±0.33</td>
<td>−1.37±0.39</td>
</tr>
<tr>
<td>LDL</td>
<td>2.87±0.56</td>
<td>4.10±0.64</td>
</tr>
<tr>
<td>HDL</td>
<td>0.05±0.33</td>
<td>−0.93±0.40</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>−6.15±1.03</td>
<td>−9.58±1.15</td>
</tr>
</tbody>
</table>

*Table 2. Changes in Efficacy and Safety End Points between Baseline and 1 Year.*

Naltrexone SR/Bupropion SR

• Concerning side effects: increased blood pressure and pulse, seizures, suicidal ideation.
• Common side effects: nausea, constipation, diarrhea, headache, dry mouth
• Stop if clinically significant increase in BP or P
• Weight loss 5-8% on average
• Intermediate effectiveness and side effects
Naltrexone SR/Bupropion SR: COR II Trial

TG decreased 9.8%
HDL increased 3.6%
LDL decreased 6.2%

1,496 subjects, 54% follow up at 1 year

Liraglutide 3mg

- GLP-1 agonist already used for glucose lowering in diabetes
- 3 mg dose approved for weight loss by FDA on 12/23/2014
- 6-8% weight loss
- Side effects: nausea, diarrhea, vomiting, pancreatitis, questions about medullary thyroid carcinoma risk
- Intermediate effectiveness, clinicians used to prescribing for diabetes
Liraglutide: Effects on Weight

Figure 2: Change in bodyweight
Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward.

Lancet 2009; 374: 1606–16
Liraglutide: Effects on “Metabolic Syndrome”

“no significant effect on lipids”

14 week study
Tg decreased 19%
LDL decreased 9.6%
HDL decreased 3%

Behavior+Medication better than either alone

Variability in Response to a Weight Loss Intervention

Ravussin E; Obesity (Silver Spring). 2009 Sep;17(9):1736-43
How to Think about Weight loss Then?

• Obesity might be thought of as one of several cardiovascular risk factors that you could choose to treat.
• Obesity is likely important early in the course of the development of CVD and may become less important later.
• There is tremendous variability in the response to treatments and so individualizing is important.
• Patients may value weight loss more than the treatment of other CVD risk factors.
### Summary of Data

#### Table 2. Summary of percent changes in cardiovascular and metabolic risk factors*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>FG (mg/dL)</th>
<th>HbA1c (%)</th>
<th>LDL (%)</th>
<th>TGL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenetermine</td>
<td>Randomized controlled trials:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no 1-year data, none since</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>1980s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlistat</td>
<td>XENDOS^59</td>
<td>7.3^† (5.2)</td>
<td>-3.6^† (-2.6)</td>
<td>1.8^† (3.6)</td>
<td>NA</td>
<td>-11.4^† (-1.6)</td>
<td>-6.2 (-6.3)</td>
</tr>
<tr>
<td>Lorcaner (10 mg BID)</td>
<td>BLOOD^46</td>
<td>1.4^† (0.8)</td>
<td>-1.1^† (-0.6)</td>
<td>-0.8^† (1.1)</td>
<td>-0.04^† (0.03)</td>
<td>2.87^† (4.03)</td>
<td>-6.15^† (-0.14)</td>
</tr>
<tr>
<td>Lorcaner (10 mg BID)</td>
<td>BLOSSOM^48</td>
<td>1.9 (1.2)</td>
<td>-1.9 (1.4)</td>
<td>NA</td>
<td>0.19 (-0.14)</td>
<td>0.3 (1.7)</td>
<td>-4.3 (-0.9)</td>
</tr>
<tr>
<td>Lorcaner (10 mg BID)</td>
<td>BLOOD-DM^47</td>
<td>0.8 (0.9)</td>
<td>1.1 (0.7)</td>
<td>-27.4^† (-11.9)</td>
<td>-0.9^† (-0.4)</td>
<td>4.2 (5.0)</td>
<td>-10.7 (-4.8)</td>
</tr>
<tr>
<td>Phenetermine/Topiramate</td>
<td>EQUIP^50</td>
<td>2.9 (0.9)</td>
<td>-1.5^† (0.4)</td>
<td>-0.6^† (1.9)</td>
<td>NA</td>
<td>-8.4^† (-5.5)</td>
<td>-5.2^† (9.1)</td>
</tr>
<tr>
<td>Phenetermine/Topiramate</td>
<td>CONQUER^51</td>
<td>5.6^† (2.4)</td>
<td>-3.8^† (-2.7)</td>
<td>-1.26^† (0.54)</td>
<td>-0.1^† (0.1)</td>
<td>-6.9^† (-4.1)</td>
<td>-10.6^† (4.7)</td>
</tr>
<tr>
<td>(15/92 mg)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bupropion/naltrexone (32/360 mg)</td>
<td>COR-I^52</td>
<td>0.1^† (1.9)</td>
<td>0.0 (-0.9)</td>
<td>3.24^† (-1.26)</td>
<td>NA</td>
<td>-2.0 (-0.5)</td>
<td>-12.7^† (-3.1)</td>
</tr>
<tr>
<td>Bupropion/naltrexone (32/360 mg)</td>
<td>COR-II^53</td>
<td>0.6^† (0.5)</td>
<td>0.4 (0.3)</td>
<td>-2.8 (-1.3)</td>
<td>NA</td>
<td>-6.2 (-2.1)</td>
<td>-9.8 (-0.5)</td>
</tr>
<tr>
<td>Bupropion/naltrexone (32/360 mg)</td>
<td>COR-BMOD^54</td>
<td>1.3^† (3.9)</td>
<td>-1.4^† (-2.8)</td>
<td>-2.4 (-1.1)</td>
<td>NA</td>
<td>7.1 (10.0)</td>
<td>-16.6^† (-8.5)</td>
</tr>
<tr>
<td>Bupropion/naltrexone (32/360 mg)</td>
<td>COR-D^55</td>
<td>0.0 (1.1)</td>
<td>-1.1 (-1.5)</td>
<td>-11.9 (-4.0)</td>
<td>-0.6^† (-0.1)</td>
<td>-1.4 (0.0)</td>
<td>-11.2^† (-0.8)</td>
</tr>
<tr>
<td>Linaclutide (3 mg)</td>
<td>Phase II^56</td>
<td>4.9 (1.6)</td>
<td>-2.8 (-0.2)</td>
<td>-5.77^† (1.44)</td>
<td>-0.26^† (0.01)</td>
<td>-0.43^† &lt;(0.28) mmol/L</td>
<td>-0.14^† &lt;(0.01) mmol/L</td>
</tr>
<tr>
<td>Linaclutide (3 mg)</td>
<td>SCALE Maintain^57</td>
<td>0.2^† (2.8)</td>
<td>1.4 (1.2)</td>
<td>-9.0^† (-3.6)</td>
<td>-0.1^† (0.1)</td>
<td>0.2^† (0.3)</td>
<td>0.0^† (0.1)</td>
</tr>
<tr>
<td>Linaclutide</td>
<td>SCALE Obesity^60</td>
<td>-2.7</td>
<td>-3</td>
<td>-7.2</td>
<td>-0.3</td>
<td>-0.09 mmol/L</td>
<td>-0.11 mmol/L</td>
</tr>
</tbody>
</table>

*Estimated treatment differences: SBP, -2.8, DBP, -0.9 mm Hg; Low-density lipoprotein cholesterol -2%, high-density lipoprotein cholesterol 2%, triglyceride levels, 9%; Progression to prediabetes: linaclutide 3 mg, 6.9%; placebo, 19.9%.
Long term phentermine prescribing

- If patient has no evidence of serious cardiovascular disease
- No serious psychiatric disease
- Has been told of the other FDA approved weight loss medications and has been told that phentermine does not have long term safety or efficacy data and that prescribing is ‘off label’
- No clinically significant increase in pulse of BP
- Pt loses at least 5% of baseline weight

J Clin Endocrinol Metab. 2015 Feb;100(2):342-62